SYNTHESIS OF NOVEL ANALOGUES OF PARACETAMOL AND THEIR PHARMACOLOGICAL EVALUATION IN NEPHROPATHY, CARDIOPATHY AND NEUROPATHY

Synopsis submitted for the award of the degree of

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CERTIFICATE

This is certified that the synopsis of Manju Jakhar (Registration No. 23DPH003), Ph.D. Research Scholar (Pharmaceutical Sciences) of the School of Pharmacy and Emerging Sciences (SPES) has been finalized and approved in consultation with Research Guiding Committee. The research scholar has successfully delivered her synopsis entiltled, "Synthesis of Novel Analogues of Paracetamol and their Pharmacological Evaluation in Nephropathy, Cardiopathy and Neuropathy," on 18.12.2024 in accordance with the academic regulation. The suggestions given by the members have been duly incorporated.

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1. INTRODUCTION

The COVID-19 pandemic, caused by the world's second most common influenza virus strain (SARS-CoV-2), began in late 2019 and has become a major public health issue. Although vaccines and other medical interventions have significantly reduced the impact of the virus, COVID-19 still remains a serious threat and new complications continue to emerge as the disease spreads. Despite progress in fighting the pandemic, COVID-19 remains a concern. This requires constant vigilance and the development of vaccines and new drugs to treat and reduce the impact of the disease. Nitric oxide (NO) is known for its role in fighting COVID-19. Nitric oxide (NO) has emerged as a potential therapeutic intervention in the treatment of COVID-19 due to its ability to restore oxygen delivery by normalizing shunting and ventilation/perfusion disorders and inhibiting respiratory coronavirus replication **(Rajendran *et al.*, 2022; de Mel 2020; Chadha *et al.*, 2023 and Ricciardolo *et al.*, 2020).**

COVID-19 triggers an inflammatory response, leading to respiratory problems and damage to many organs. Nitric oxide has anti-inflammatory properties that can reduce this problem. This is especially important for COVID-19 patients who suffer from shortness of breath and hypoventilation. Reduces the formation of blood clots. COVID-19 increases the risk of blood clots, which can lead to serious complications such as pulmonary embolism and stroke. Nitric oxide is an antithrombotic agent that reduces blood clots.

Paracetamol has been reported to have hepatotoxicity therefore, its long-term use has not been recommended. Bhardwaj and associates have prepared nitric oxide releasing analogues of paracetamol which have been found to have hepatoprotection and also enhanced therapeutic effects **(Bhardwaj *et al.*, 2012).** Taking into consideration nitric oxide's roles in various ailments it was considered of interest to explore its protective roles against nephropathy, cardiopathy and neuropathy.

1.1 Role of Nitric Oxide in Physiological Processes

Nitric oxide (NO) is a vital signalling molecule that plays an essential role in regulating physiological processes across multiple systems. Its actions span from vascular regulation to immune modulation and tissue repair **(Mirzaei & Khazaei 2017).**

- **Cardiovascular System:** NO is essential for vasodilation, regulating blood pressure, and maintaining endothelial function. It helps reduce the risk of atherosclerosis by inhibiting platelet aggregation and smooth muscle cell proliferation.

- **Nervous System:** NO acts as a neurotransmitter, facilitating synaptic plasticity and modulating neural communication. It also helps in maintaining cerebral blood flow and protecting the brain

from hypoxia-induced damage.

- **Immune System:** NO plays a role in immune responses, particularly in the defense against pathogens. It helps in the killing of microbes and the regulation of immune cell activity.

- **Gastrointestinal System:** NO regulates gut motility, mucosal blood flow, and the secretion of digestive enzymes. It aids in controlling smooth muscle tone and maintaining gut integrity.

- **Reproductive System:** In the reproductive system, NO is involved in the regulation of blood flow to reproductive organs, influencing processes like erection in males and uterine contractility in females.

- **Respiratory System:** NO plays a key role in regulating airway tone, promoting bronchodilation, and controlling blood flow in the lungs, improving oxygen exchange.

- **Renal System:** NO is vital for regulating renal blood flow, glomerular filtration rate, and sodium balance. It helps in the prevention of kidney damage and in the regulation of blood pressure.

- **Wound Healing:** NO promotes tissue repair by enhancing collagen synthesis, cell proliferation, and angiogenesis, aiding in the healing process.

- **Cytotoxicity:** NO exhibits cytotoxic properties, particularly in immune defense, where it helps kill infected or cancerous cells through oxidative mechanisms.

- **Eye System:** In the eyes, NO is involved in regulating ocular blood flow, intraocular pressure, and preventing retinal damage, contributing to overall visual health.

1.2. COVID-19 Pandemic

- **Trigger & Effects**:
  SARS-CoV-2 → Inflammatory response → Respiratory issues and multi-organ damage
- **Symptoms**: Fever, cough, shortness of breath, fatigue, body aches, loss of taste/smell
  Severe cases: Respiratory distress, organ failure
- **Origin and Impact**:
  - Began in late 2019, caused by SARS-CoV-2
  - Major public health issue despite vaccines and interventions
  - Continuous emergence of complications → need for vigilance and new treatments
- **Populations at Higher Risk for COVID-19:**
  Elderly (aged 60+)
- **Individuals with pre-existing health conditions:**

- Cardiovascular disease (cardiopathy)
- Diabetes (nephropathy)
- Chronic respiratory diseases (e.g., COPD)
- Immunocompromised individuals (e.g., HIV/AIDS)

Like COVID-19, other viral infections also cause widespread health challenges and require targeted treatments **(Iwasaki *et al.*, 2021; Mokibel *et al.*, 2023)**

- **Influenza (Flu)**: Respiratory issues similar to COVID-19
- **SARS (SARS-CoV)**: Severe respiratory symptoms and high mortality rates
- **MERS (MERS-CoV)**: Multi-organ damage and respiratory failure
- **HIV/AIDS**: Immune system suppression requiring lifelong treatment
- **Dengue**: Fever, joint pain, and systemic inflammation

1.3. Nitric Oxide – Applications and Significance in COVID-19 and Other Viral Infections

1.3.1. Role in COVID-19:

- Improving Oxygen Delivery
- Inhibiting Viral Replication
- Anti-inflammatory properties
- Blood Clot Prevention

1.3.2. Significance in Other Viral Infections:

- Influenza (Flu)
- SARS and MERS
- HIV/AIDS
- Dengue

Nitric oxide holds promise as a therapeutic tool not only for COVID-19 but also for other viral infections due to its ability to modulate inflammation, inhibit viral replication, and reduce blood clotting **(Rajendran *et al.*, 2022; Lisi *et al.*, 2021).**

2. LITERATURE REVIEW

Nitric oxide (NO) is a crucial signalling molecule in the human body, regulating various physiological and pathological processes in cells and tissues. In the year 1992, Nitric oxide was designated as **"Molecule of the Year"** on account of its exceptional biological properties **(Stamler *et al.,* 1992).** Its diversified roles in maintaining blood pressure, stimulating the immune system, regulating neural transmission, gene expression, platelet aggregation, learning and memory, gastroprotection, male sexual function, cytoprotection and in inflammations have been extensively studied and established. The work related to nephropathy, cardiopathy and neuropathy reported in the literature is discussed next.

2.2. Previous Studies:

Bhardwaj *et al.* (2012) developed NO-releasing analogues of paracetamol, which were found to be effective hepatoprotective agents.

These analogues showed encouraging results against liver toxicity, enhancing the therapeutic effects of paracetamol while protecting the liver.

2.3. Nephropathy:

Ahmad *et al.,* 2018 In addition to being essential for controlling glomerular and medullary hemodynamics, nitric oxide may also have an impact on the development of renal illnesses.

Tessari 2015 Progressive NO deficit is linked to late diabetic nephropathy, whereas enhanced intrarenal NO production is linked to hyperfiltration and microalbuminuria in early diabetic nephropathy.

Carlstrom & M. 2021 Nitric oxide (NO) is linked to the development and progression of kidney disease and cardiometabolic complications. A study found that nitrate supplementation can lower blood pressure, particularly in hypertensive or diabetic patients with CKD. However, this effect is not significant in healthy individuals. Future randomized trials are needed to determine if supplementation with inorganic nitrate and/or nitrite could be a beneficial additive treatment to slow the progression of kidney disease and associated cardiovascular and metabolic disorders.

2.4. Cardiopathy:

Infante *et al.,* 2021 By controlling blood pressure, and vascular tone, blocking platelet aggregation, and halting the proliferation of smooth muscle cells, nitric oxide plays a critical role in avoiding the development and progression of cardiovascular disease.

Tran *et al.*, 2022 Endothelial, neuronal, and inducible enzymes play important roles in controlling blood pressure, preventing endothelial dysfunction, and reacting to vascular injury, stroke, and cerebral ischaemia. Nitric oxide is involved in these processes in the cardiovascular system.

Sun *et al.*, 2020 discovered that HNO has antiapoptotic, anti-hypertrophic, and antioxidant properties that can alleviate hyperglycemia-induced myocardial damage. However, the colocalization of Cav-3 and the phosphorylation of exogenous HNO were reduced after high glucose exposure.

Ma *et al.*, 2021 reviewed the potential of nitric oxide (NO) release platform, inhaled NO therapy, and stem cell therapy in treating cardiovascular disease. They highlighted the development of chitosan hydrogel-enhanced therapeutic function in hindlimb ischemia.

Kamenshchikov *et al.*, 2019 found that nitric oxide delivery to the cardiopulmonary bypass circuit during cardiac surgery decreases levels of heart-specific blood markers and provides cardioprotection.

Akopova *et al.*, 2022 reported that the catalytic activity of NOS on the precursor L-arginine results in the production of NO, which can be low or high output, depending on the enzyme. All three NOS isoforms have been found in the human myocardium and have been proven to be induced in reaction to hypoxia or ischaemia.

Hamarneh *et al.*, 2022 suggested that NO is sufficient to generate late preconditioning (PC) and that nitrates might be employed in the therapeutic setting as a PC-mimetic treatment for the prevention of ischemia damage.

2.5. Neuropathy:

Rezaei *et al.*, 2022 reported that NO functions as a signalling molecule that contributes to neuroprotection at physiological levels. It supports blood flow maintenance, synaptic plasticity regulation, and neural communication modulation.

Larson *et al.*, 2014 reported that Hypoxia neuroprotection mechanisms in natural systems aid stroke patient resistance. Insights from hypoxia-tolerant species guide clinical brain injury management. NO contributes to neuroprotection by regulating cerebral blood flow, helping maintain brain oxygenation and preventing hypoxia-induced brain injuries.

Tripathi *et al.*, 2020 discuss the role of nitric oxide (NO) in the central nervous system, specifically in autism spectrum disorder (ASD) and other brain disorders. NO, produced from l-arginine by nitric oxide synthase, is involved in neurodevelopmental and neurodegenerative

disorders through SNO signalling. Aberrant SNO may contribute to ASD and other neurodevelopmental disorders. NO signalling dysregulation can also induce various neuropsychiatric and neurological disorders.

Mangal *et al.*, 2023 focus on reactive nitrogen species (RNS) and reactive oxygen species (ROS), which can lead to cell death and are involved in the pathogenesis of cognitive impairments and neural injury. Elevated NO production, which occurs in neurodegenerative diseases, inflammation, and ischemia, can be targeted for therapeutic intervention. Naturally occurring polyphenols that target the NO signalling pathway may be significant in neurodegeneration and related complications.

2.6. COVID-19:

Nitric oxide has shown potential as a promising treatment for COVID-19, inhibiting viral replication and potentially playing a crucial role in pathogen control **(Lisi *et al.*, 2021)**

Zhang and co-workers have reported non-invasive treatment based on nitric oxide against sars- cov-2 and COVID-19. Nitric oxide (NO) has an antiviral effect confirmed in the 1990s. Recent studies show the potential of NO in the treatment of the coronavirus disease 2019 (COVID-19) and SARS-CoV-2 pandemics. This review explores the molecular mechanisms underlying the NO-based therapy for SARS **(Zhang *et al.*, 2023)**

According to Mekontso and associates' studies patients with refractory ARDS who were no longer eligible for ECMO after iNO treatment had reduced death rates, indicating that iNO may improve outcomes for C-ARDS patients. iNO enhances oxygenation, particularly in severe C-ARDS cases, and benefits ECMO-eligible patients by increasing survival rates in resistant ARDS. Their study examines the use, response, and outcomes of inhaled nitric oxide in COVID-19 ARDS patients **(Mekontso *et al.*, 2023)**

3. AIM AND OBJECTIVE

Taking to consideration significate role of nitric oxide, it was envisaged to synthesize nitric oxide releasing analogues of paracetamol with the aim to have protection in nephropathy, cardiopathy and neuropathy in elderly patients suffering from COVID-19 or viral infections.

RATIONALE

The novel nitric oxide-releasing paracetamol derivatives molecule integrates the analgesic and antipyretic properties of paracetamol with the vasodilatory and anti-inflammatory effects of nitric oxide, demonstrating potential protective effects on critical organs affected by COVID-19, such as the lungs and heart. These derivative holds promise in enhancing oxygenation, mitigating inflammation, and improving respiratory function, thereby potentially attenuating the severity of acute respiratory distress syndrome (ARDS) in severe COVID-19 cases. Furthermore, nitric oxide's vasodilatory properties could potentially benefit patients with cardiovascular disorders by improving blood flow and reducing strain on the heart. In individuals with diabetes, nitric oxide's role in enhancing insulin sensitivity and vascular function may offer protective effects against COVID-19-related complications. For patients with neurological disorders, nitric oxide's neuroprotective properties might mitigate neuroinflammation and oxidative stress induced by the virus, potentially improving outcomes.

Additionally, the paracetamol component of this derivative aids in fever and pain management, thereby enhancing overall patient comfort and supporting recovery. Amid the diverse treatment regimens available for COVID-19, none have yet been specifically highlighted for significant efficacy. Notably, most COVID-19 fatalities occur in patients with pre-existing diabetes, cardiovascular, and neurological conditions.

Therefore, there is dire need for the novel drug to be used in the treatment of COVID-19 and other viral infections. In addition, it is also required for patients suffering from nephropathy, cardiopathy and neuropathy.

4. PROPOSED WORK PLAN

The expected duration of the proposed work is 3 years.

- The first year will be dedicated to the preparation phase for the literature review, procurement ofrequirements and **Chemical Reaction & Evaluation.**
- The second year will be mainly focused on the experimentation work
- In the last year, all the data will be collected and analysed statistically and conclude.A detailed overview of the proposed work timeline is given below;

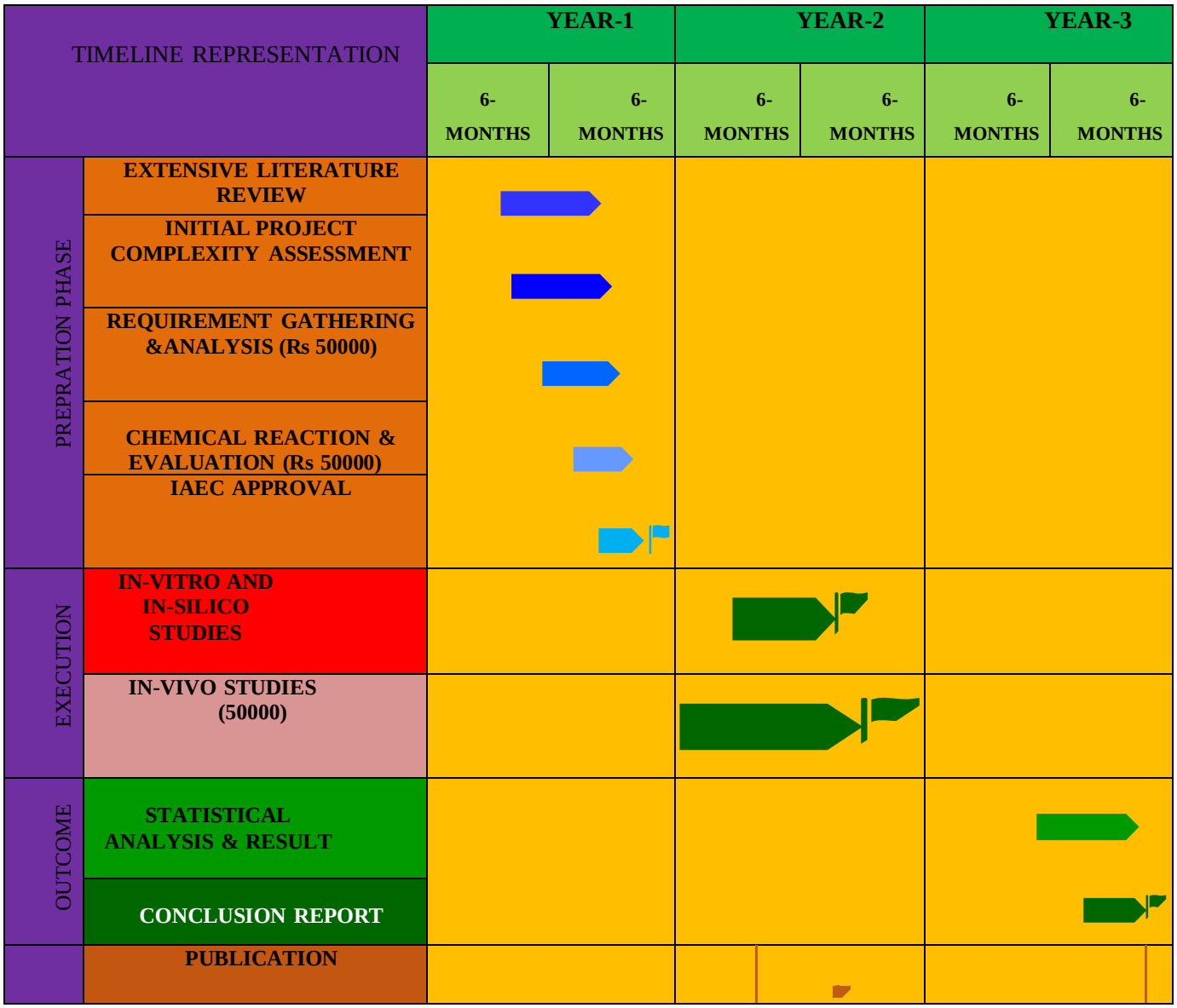

Figure 4. Detailed Timeline for PHD Research Work

5. RESEARCH METHODOLOGY

The proposed research work is discussed under the heads

5.1. Synthesis of novel analogues of Paracetamol

The nitric oxide-releasing paracetamol analogues will be synthesized by using the procedure reported by Mehta and associates (**Mehta, N. 2007)** given below:

1.1: *N*-[4-(2-Bromoethoxy)phenyl]acetamide

1.2: *N*-[4-(2-Nitrooxyethoxy)phenyl]acetamide

2.1: *N*-[4-(3-Bromopropoxy)phenyl]acetamide

2.2: *N*-[4-(3-Nitroxypropoxy)phenyl]acetamide

3.1: *N*-[4-(5-Bromopentyloxy)phenyl]acetamide

3.2: *N*-[4-(5-Nitroxypentyloxy)phenyl]acetamide

5.2. Characterization of nitric oxide-releasing paracetamol analogues

The nitric oxide releasing paracetamol analogues will be characterised by sophisticated analytical techniques such as: UV, IR NMR Mass spectrometry etc.

5.3. Molecular modelling and docking studies

In silico docking studies of the paracetamol analogues with various enzymes and proteins present in the kidneys, heart and brain will be evaluated by this method. Pharmacophore models of superoxide dismutase and acetyl-cholinesterase will be used for screening. The virtual docking software Molergo Molecule Virtual Docker and the protein data bank will be utilized to assess the docking score and affinity of the test molecule. **(Rani *et al.*, 2022).** The results so obtained will be utilized for comparison with the biological studies as well as the development of new analogues

5.4. Biological evaluation

- **Animal models**

Adult Albino Wistar rats for nephropathy, cardiopathy, and Swiss albino mice will be used for neuropathy and provided by the Central Animal House. School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, Solan, Himachal Pradesh-173205.

The experimental details concerning biological evaluation will be carried out as given below:

i. Nephropathy:

Table 1. Group Plan for Diclofenac-Induced Nephrotoxicity in Albino Rat.

Group		Treatment	Animal Count	Dose (mg/kg)
I	Control	Normal Saline	6	-
II	Diseased	Diclofenac	6	As per Literature
III	Standard	Diclofenac + Fosinopril	6	As per Literature
IV	Test I	Diclofenac + Test Derivative-1	6	As per Literature +100mg
V	Test II	Diclofenac + Test Derivative-1	6	As per Literature + 200 mg
VI	Test III	Diclofenac + Test Derivative-2	6	As per Literature +100mg
VII	Test IV	Diclofenac + Test Derivative-2	6	As per Literature + 200 mg

The nephroprotective studies will be carried out by:

- Measurement of serum creatinine and blood urea nitrogen (BUN).
- Urinalysis to assess proteinuria, hematuria, and other markers.
- Histopathological Examination for signs of inflammation, fibrosis, and structural changes.

ii. Cardiopathy:

Table 2. Group Plan for Doxorubicin-Induced Cardiotoxicity in Albino Rat

Group		Treatment	Animal Count	Dose (mg/kg)
I	Control	Normal Saline	6	-
II	Diseased	Doxorubicin	6	As per Literature
III	Standard	Doxorubicin + Prophylactically	6	As per Literature
IV	Test I	Doxorubicin + Test Derivative-1	6	As per Literature +100mg

V	Test II	Doxorubicin + Test Derivative-1	6	As per Literature + 200 mg
VI	Test III	Doxorubicin + Test Derivative-2	6	As per Literature +100mg
VII	Test IV	Doxorubicin + Test Derivative-2	6	As per Literature + 200 mg

The cardioprotective studies will be carried out by:

- Measurement of cardiac biomarkers such as troponins and B-type natriuretic peptide (BNP).
- Histopathological Examination of heart tissue for signs of hypertrophy, fibrosis, and inflammation.
- Assessment of oxidative stress markers in cardiac tissue.
- Histopathological Examination

iii. Neuropathy:

Table 3. Group Plan for Scopolamine-Induced Neurotoxicity in Swiss Albino Mice

Group		Treatment	Animal Count	Dose (mg/kg)
I	Control	Normal Saline	6	-
II	Diseased	Scopolamine	6	As per Literature
III	Standard	Imipramine + Scopolamine	6	As per Literature
IV	Test I	Scopolamine+ Test Derivative-1	6	As per Literature +100mg
V	Test II	Scopolamine + Test Derivative-1	6	As per Literature + 200 mg
VI	Test-III	Scopolamine + Test Derivative-2	6	As per Literature +100mg
VII	Test-IV	Scopolamine + Test Derivative-2	6	As per Literature +200mg

The neuroprotective studies will be carried out by:

- Antidepressant activity will be performed by using the forced swim test model.
- Anxiolytic activity will be performed using the Elevated Plus Maze model.
- Exploratory behaviour patterns will be performed by the Head dip test method.

- CNS inhibitory activity will be performed using an Actophotometer.
- Histopathological Examination

Since COVID-19 has not been completely eradicated and remains the main cause of death particularly in diabetic patients suffering from nephropathy, cardiopathy and neuropathy, Therefore, there is dire need for the protection of heart, brain and kidney of the Covid-19 or virally infected patients. The purposed paracetamol analogues are expected to have nephroprotection, cardioprotection and neuroprotection on account of their nitric oxide releasing properties, in addition to their hepatoprotection thus will significant role with respect to their potential applications in COVID-19 patients and viral infected patients.

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